Inflammation and intracranial aneurysms: mechanisms of initiation, growth, and rupture

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ABSTRACT

Outcomes following aneurysmal subarachnoid hemorrhage remain poor in many patients, despite advances in microsurgical and endovascular management. Consequently, considerable effort has been placed in determining the mechanisms of aneurysm formation, growth, and rupture. Various environmental and genetic factors are implicated as key components in the aneurysm pathogenesis. Currently, sufficient evidence exists to incriminate the inflammatory response as the common pathway leading to aneurysm generation and rupture. Central to this model is the interaction between the vessel wall and inflammatory cells. Dysfunction of the endothelium and vascular smooth muscle cells (VSMCs) promotes a chronic pathological inflammatory response that progressively weakens the vessel wall. We review the literature pertaining to the cellular and chemical mechanisms of inflammation that contribute to aneurysm development. Hemodynamic stress and alterations in blood flow are discussed regarding their role in promoting chronic inflammation. Endothelial cell and VSMC dysfunction are examined concerning vascular remodeling. The contribution of inflammatory cytokines, especially tumor necrosis factor-α is illustrated. Inflammatory cell infiltration, particularly macrophage-mediated deterioration of vascular integrity, is reviewed. We discuss the inflammation as a means to determine aneurysms at greatest risk of rupture. Finally, future therapeutic implications of pharmacologic modulation of the inflammation are discussed.

Key words: Aneurysm, endothelium, inflammation, subarachnoid hemorrhage, vascular smooth muscle cells

INTRODUCTION

Intracranial aneurysms and subarachnoid hemorrhage (SAH) represent significant disease entities, with ruptured aneurysms accounting for severe disability and death in approximately 27,000 Americans each year.[1] Among the general population, approximately 4-5% of individuals harbor an unruptured aneurysm.[2] However, with the evolution of sophisticated imaging modalities, such as magnetic resonance imaging (MRI), magnetic resonance angiography, and computed tomographic angiography, unruptured incidental aneurysms are continually discovered with increasing frequency. Microsurgical and endovascular obliteration remains the mainstays of treatment, yet both are associated with a significant risk of morbidity and mortality.[3,4] In addition, a significant number of unruptured aneurysms are treated preemptively to avoid the catastrophic sequelae associated with SAH. Despite the prevalence of these lesions, the often-devastating nature of the disease, and the risks associated with treatment, relatively little is known about the aneurysm pathogenesis and natural history. As a result, there has been a significant effort to define the mechanisms underlying aneurysm formation and growth. Although the evolution of aneurysms from initiation to rupture is undoubtedly multifactorial in nature, the inflammatory response appears to play a critical role in the pathogenesis of these lesions.

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Further understanding of the relationship between the inflammatory response and aneurysm evolution may have important clinical implications in the future. Identification of patients prone to pathologic inflammatory states could allow detection of a population more likely to suffer aneurysm rupture. Additionally, the genetic and cellular processes mediating inflammation represent attractive targets for possible pharmacologic intervention. We review the current literature pertaining to the role of inflammation in the generation of aneurysm formation and rupture. The various vascular inflammatory stimuli are discussed, with special attention paid to hemodynamic stress and alterations in blood flow. Endothelial cell

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and vascular smooth muscle cell (VSMC) dysfunction are detailed and examined in relation to vascular remodeling. The contribution of multiple cytokines to a sustained pathologic inflammatory state and their influence on aneurysm formation are outlined. Special emphasis is placed on a key inflammatory mediator, tumor necrosis factor-α (TNF-α). The contribution of inflammatory cell infiltration, particularly the potential of macrophage-mediated rupture, is detailed. Finally, future therapeutic implications of pharmacologic modulation of the inflammatory response are discussed.

INTRACRANIAL ANEURYSMS AND THE INFLAMMATORY RESPONSE

Multiple studies have identified various risk factors for aneurysmal expansion and rupture.[5] Genetics plays an important role, with approximately 10% of SAH patients having two or more family members also affected by unruptured or ruptured aneurysms.[6,7] The propensity for SAH within specific ethnic groups, particularly the Finish and Japanese populations, further highlights the contribution of genetics.[8,9] Gender also appears to play a role, as women appear to more frequently develop intracranial aneurysms and perhaps suffer from ruptured aneurysms more often than men.[10,11] Environmental factors, particularly smoking, have been clearly linked to a higher incidence of SAH.[11] Additional studies have linked binge drinking to aneurysm rupture.[12,13] Chronically uncontrolled hypertension clearly correlates with aneurysm formation in animal models and clinical studies have identified hypertension as a risk factor for aneurysmal SAH.[10,11,14-16]

Due to the variability in contributing risk factors, attempts have been made to identify a unifying underlying pathophysiologic mechanism that promotes aneurysm formation and rupture.[5] There is a tremendous mounting body of evidence that the inflammatory response represents a common endpoint that drives aneurysm evolution, which is succinctly summarized as initiation of development, growth, and potential rupture.[17] Hemodynamic stress and disruption of blood flow, oxidative stress, injurious environmental elements (i.e. cigarette smoking and cocaine), and pro-inflammatory genetic alterations all initiate a sustained and pathologic inflammatory response.[18,19] As a result, the intracranial vasculature is subjected to endothelial cell dysfunction, elevated inflammatory cell infiltration, detrimental changes within the tunica media, and exposure to increased concentrations of proteases. These processes lead to weakening, dilation, and remodeling of the vessel walls, which are key components in aneurysm formation and rupture.

ENDOTHELIAL CELL DYSFUNCTION, VASCULAR REMODELING, AND INFLAMMATION

Vascular remodeling is a complex process that is driven, in large part, by hemodynamic stresses along vessel walls.[18] The propensity for aneurysms to form at vessel branch points and the association of aneurysms with environmental stimuli known to disrupt vascular integrity (smoking, hypertension) highlights the role of abnormal blood flow and shear stress in aneurysm formation.[17] High wall shear stress has been shown to initiate activation of the inflammatory response.[20-22] Central to this process is the endothelial cells, which act as an interface between blood flow and the vessel wall.[17] Through the process of mechanotransduction, these cells respond to the mechanical stimuli of shear, stretch, and flow by altering their physical structure and initiating biologic signaling.[23-25] Multiple mechanical sensors have been identified, including, ion channels, integrins, cell adhesion molecules, and G protein-coupled receptors at the apical and basal surfaces of endothelial cells.[26-29] Activation of these sensors initiates intracellular cascades that result in a sustained inflammatory response [Table 1].

Aoki *et al.*[30] demonstrated a direct link between shear stress and activation of the inflammatory cascade in a rat model. Cyclooxygenase-2 (COX-2) activity, which is induced by hemodynamic force, generates prostaglandin E2 (PGE2), leading to activation of the pro-inflammatory mediator nuclear factor-κB (NF-κB).[30] Inflammation is then sustained through a positive feedback loop containing PGE2 and NF-κB, creating an environment in which vessel wall degradation can occur. Inhibition of COX-2 or loss of the PGE2 Rp suppressed NF-κB-mediated chronic inflammation and was associated with a decreased incidence of cerebral aneurysms. Additional support for the role of NF-κB-mediated pathways in inflammation-induced aneurysm formation is found in diminished aneurysm formation and growth in rats treated with statins, which inhibit NF-κB activity.[31-33]

Evidence also exists that implicates angiogenesis secondary to inflammation-driven endothelial cell dysfunction as a significant contributor to aneurysm formation. The presence of angiogenic growth factors, including, vascular endothelial growth factor (VEGF) and basic fibroblast growth factor, within aneurysm walls has been well documented within the literature.[34] In pathologic states VEGF induces changes in the endothelium leading to increased permeability at intercellular junctions and activation of pathways resulting in the breakdown of the tunica media and extracellular matrix.[35,36] Importantly, VEGF may also

Table 1: Summary of the role of inflammatory mediators in aneurysm growth and rupture

	Endothelial cells	Vascular smooth muscle cells	Macrophages
Role in vascular homeostasis	Interface between blood flow and vessel wall Mechanotransduction Respond to shear stress and flow	Contractile state maintains vessel wall integrity	M2 subset is antiinflammatory Play a role in vascular repair
Associated cell signaling molecules (secreted by or possess receptors for)	VEGF bFBF SDF-1 COX-2 PGE2 NF-κB TNF-α	NF-κB MMPs IL-1β MCP-1 TNF-α	MMPs Elastases MCP-1 NF-κB TNF-α
Role in aneurysm formation	Migration grants inflammatory cells increased access to vessel wall Proliferation/neovascularization leads to increased inflammatory cell access to vessel wall Complex cell signaling leading to chronic inflammatory state	Secretory phenotype leads to inflammatory state Erratic migration Apoptosis Weakening of vessel wall	Propagate inflammatory response May play significant role in progression to rupture Release elastases and MMPs involved in vessel wall degradation

VEGF: vascular endothelial growth factor; bFBF: basic fibroblast growth factor; SDF-1: stromal cell-derived factor-1; COX-2: cyclooxygenase-2; PGE2: prostaglandin E2; NF-κB: nuclear factor-κB; TNF-α: tumor necrosis factor-α; MMP: matrix metalloproteinases; IL-1β: interleukin-1β; MCP-1: monocyte chemoattractant protein-1

initiate the genesis of new capillary tubes, microvascular sprouting, and maturation of proliferating vessels.[37-39] bFGF targets endothelial cells, fibrocytes, and myocytes and mediates vascular wall maturation during angiogenesis.[40-43] Hoh *et al.*[44] recently reported on the expression of stromal cell-derived factor-1 (SDF-1), a chemokine with pro-angiogenic and pro-inflammatory properties, in the walls of human and murine intracranial aneurysms. SDF-1 promoted endothelial cell migration and proliferation, as well as capillary tube formation in *in vitro* studies.

Vessel proliferation within aneurysm walls is a proposed mechanism by which inflammatory cells gain increased access to the underlying tunica media, thereby accelerating degradation of this layer. The vaso vasorum is typically not present in the intracranial vasculature, with the exception of the proximal intracranial carotid and vertebral arteries.[45] However, multiple case reports have described the presence of an extensive vaso vasorum with the walls of intracranial aneurysms.[44,46,47] Neovascularization in these cases was also associated with inflammatory cell invasion on histopathologic examination.

INFLAMMATION-DRIVEN DEGRADATION OF VASCULAR SMOOTH MUSCLE AND THE EXTRACELLULAR MATRIX

Under normal physiologic conditions VSMCs, the primary cellular component of the tunica media, remain in a contractile state, maintaining the integrity of the vessel wall. In pathologic conditions, such as those that arise in the setting of increased hemodynamic stress, endothelial dysfunction, as well as direct VSMC injury, leads to disruption of the tunica media and extracellular matrix.[48,49] Central to this process is the VSMC transition from a contractile to a secretory phenotype defined by a loss of markers of contractility and expression of pro-inflammatory cytokines and matrix metalloproteinases (MMPs).[17,50-54] Alterations in VSMC phenotype have been reported in the setting of atherosclerotic lesions, in which these cells upregulate the production of NF-κB, secrete cytokines, release MMPs, and migrate into the intima, where proliferation results in vessel stenosis.[55,56] Interestingly, in atherosclerotic lesions where inflammation leads to VSMC migration and proliferation, intracranial aneurysm walls are defined by VSMC erratic migration and apoptosis.[48] As aneurysm formation progresses, substantial thinning of the tunica media and cellular loss is observed.[48,57,58] Ruptured aneurysms are more frequently found to have hypocellular and hyalinized walls when compared to unruptured aneurysms, highlighting the progressive nature of wall destruction.[59,60]

Multiple inflammatory cascades appear to be involved in VSMC dysfunction and death [Table 1]. Interleukin-1β (IL-1β) is a pro-inflammatory cytokine that initiates a number of deleterious effects within the VSMCs and extracellular matrix.[48] IL-1β plays an important role in recruiting inflammatory cells to atherosclerotic lesions and areas of vessel injury.[61,62] This cytokine also activates NF-κB, which is responsible for inducing inflammatory cascades, promoting pro-inflammatory gene expression, and mediating downregulation of procollagen synthesis within the tunica media.[48,63] IL-1β also directly induces apoptosis of VSMCs, thereby promoting thinning of the aneurysm wall.[48] Further supporting the role of IL-1β in VSMC degradation is the impairment of aneurysm growth in IL-1β deficient mice.[64]

Ets-1 is a transcription factor primarily activated in VSMCs residing in the tunica media.[65] Multiple

studies have shown Ets-1 to play a role in the regulation of vascular inflammation, pathologic remodeling, and angiogenesis.[66-69] Aoki *et al.*[65] demonstrated upregulation and activation of Ets-1 in intracerebral aneurysm VSMCs, strongly implicating this inflammatory transcription factor in aneurysm evolution.

Vascular smooth muscle cells in a secretory state generate increased monocyte chemoattractant protein-1 (MCP-1), a chemokine involved in the attraction and migration of monocytes and macrophages to areas of damaged tunica media.[70] MCP-1 upregulation has been demonstrated in the early stages of cerebral aneurysm formation in rat models, and MCP-1 blockade resulted in decreased macrophage infiltration and aneurysm progression.[71,72] Chalouhi *et al.*[73] reported high levels of MCP-1 in the lumen of unruptured cerebral aneuryms, implicating this chemokine in early aneurysm formation.

Normal maintenance of the extracellular matrix is dependent on the balance between MMPs and their inhibitors, tissue inhibitors of matrix metalloproteinases (TIMPs).[52] Imbalance in this system results in excessive breakdown of the collagen and elastin of the extracellular matrix and resultant vessel wall weakening, a key contributor to aneurysm development and rupture. MMPs and TIMPs have been linked to the development of atherosclerotic lesions and the genesis of abdominal aortic aneurysms.[12,74-80] Immunohistochemistry and western blotting have demonstrated the presence of MMPs within the walls of intracranial aneurysms.[81,82] In SAH patients, elevated serum MMP-9 levels have been documented, with normalization occurring by postbleed day 12.[83] Cigarette smoke, a well-established, inflammatory stimulus for aneurysm initiation and growth, has been demonstrated to induce macrophage differentiation and increased release of MMP-2/9.[84] In a comparison of smokers and nonsmokers, the carotids of smokers demonstrated elevated levels of MMPs and a decreased concentration of TIMPs and elastin compared to nonsmokers.[85]

Laboratory investigations also support derangement of MMP and TIMP interactions as a key component in the aneurysm pathogenesis. In a rat model, Aoki *et al.*[51] demonstrated increased levels of MMP-2 and MMP-9 in aneurysm walls, with increasing expression as aneurysms progressed. Ali *et al.*[86] reported MMP stimulation by cigarette smoke extract in rat cerebral VSMCs *in vitro* and in carotid VSCMs *in vivo*.

TUMOR NECROSIS FACTOR-α

Tumor necrosis factor-α has emerged as a potential key contributor in the generation, growth, and eventual rupture of intracranial aneurysms. Multiple studies have demonstrated increased levels of TNF-α within the cerebral circulation in response to injury or ischemia.[87,88] Elevated levels of TNF-α mRNA have been demonstrated in intracranial aneurysms with reverse transcription-polymerase chain reaction.[89] Plasma TNF-α is also increased in aneurysm patients while additional authors have reported an association between single-nucleotide polymorphisms in the TNF-α gene and an increased risk of aneurysm incidence and rupture.[90-94]

Tumor necrosis factor-α is a well-established mediator of inflammation and apoptosis, working through multiple receptors to modulate various cellular responses to injury. Tumor necrosis factor-α receptor 1 (TNFR1) primarily binds the soluble form of TNF-α and plays a central role in TNF-α-induced cellular signaling.[95,96] Importantly, TNFR1 contains a death domain that plays a role in TNF-α-mediated apoptosis.[97,98] A second receptor, TNFR2, is activated by membrane-bound TNF-α and primarily found on endothelial and immunomodulatory cells. Activation of TNFR1 signals apoptosis through the activation of the Fas-associated death domain (FADD), which in turn, binds and activates pro-caspase 8. Ultimately, this pathway leads to the activation of multiple proteases that result in apoptosis. Jayaraman *et al.*[2] postulate that a complex interaction between TNF-α and both receptors induces and promotes aneurysm growth.Initially, endothelial activation is driven by TNFR2 and membrane-bound TNF-α. Activated endothelial cells generate high concentrations of soluble TNF-α, which interacts with the TNFR1, leading to endothelial cell dysfunction and death. Endothelial cell death, in turn, creates increased vascular permeability, thereby creating multiple pathways for macrophage infiltration, MMP generation, and loss of the VSMC layer. An additional receptor, tTNF-Rp55, initiates apoptosis through the induction of caspases.[89] The TNF-Rp55 also induces the recruitment and activation of caspases through interaction with the FADD protein.[99] Documented increased expression of the FADD protein in human aneurysms also supports TNF-α-mediated apoptosis as a causative factor in aneurysm formation.[89]

Tumor necrosis factor-α also appears to play an important role in the pathologic VSMC changes observed in aneurysm formation and rupture, driving these cells to change from a contractile to a synthetic and pro-inflammatory phenotype. Furthermore, the secretory phenotype of VSMCs participates in the secretion of TNF-α when exposed to inflammatory stimuli.[100,101] Ali *et al.*[102] demonstrated TNF-α to suppress expression of contractile genes and induce the expression of pro-inflammatory genes in VSMCs

in vivo and *in vitro*. In the same study, TNF-α induced increased expression of Kruppel-like transcription factor 4, a known regulator of VSMC differentiation.[102] Additional studies have identified cigarette smoke, a known potent pro-inflammatory stimulus, to induce similar phenotypic changes in VSMCs, including increased secretion of TNF-α.[100] Clearly the data shows TNF-α secretion to be involved in a positive feedback loop with VSMCs, with TNF-α stimulating phenotypic change and thus driving its own secretion from these cells. The fact that VSMCs appear to first exhibit pathologic migration, followed by disappearance prior to rupture suggests TNF-α first induces phenotypic change that is followed by apoptosis in the presence of chronically sustained levels of the cytokine.[103]

INFLAMMATORY CELL MIGRATION AND INFILTRATION

Endothelial cell dysfunction and apoptosis increase the permeability of vessel walls, allowing for enhanced binding and transmigration of inflammatory cells into the underlying VSMC layer. T-cells have been demonstrated within aneurysm walls where they respond to antigen presentation by monocytes and macrophages.[104] In a rat model, mast cells were significantly increased within the walls of forming cerebral aneurysms.[105] Inhibition of mast cell degranulation diminished aneurysm size, prevented thinning of the tunica media, blocked NF-κB activation, and decreased expression of MCP-1, MMP, and IL-1β. An evaluation of human intracerebral aneurysms found mast cells to be significantly increased in ruptured compared to unruptured aneurysms.[106] These findings suggest mast cells play an important role in aneurysm growth and rupture.

Monocytes and macrophages appear to be essential to aneurysm formation and rupture, a finding that has been repeatedly demonstrated in animal and clinical studies. These cells secrete MMPs and elastases which are responsible for degradation of the extracellular matrix and the internal elastic lamina.[107] Kanematsu *et al*.[108] observed macrophage depletion and inhibition of MCP-1 to be associated with a reduced incidence of intracranial aneurysms. Aoki *et al*.[72] also observed a significant decrease in cerebral aneurysm formation, macrophage accumulation, and expression of MMP-2 and MMP-9 in MCP-1 deficient mice. In a murine model, Ruzevick *et al*.[109] observed the haptoglobin 2-2 (Hp2-2) genotype, which is linked to a pro-inflammatory state, to be associated with significantly larger aneurysms and a greater number of macrophages within the aneurysm walls. Histopathological examination of ruptured and unruptured human intracranial aneurysms has demonstrated macrophage infiltration within aneurysmal walls.[59,60,110] Chalouhi *et al*.[73] found high plasma concentrations of MCP-1 within the lumens of intracranial aneurysms, suggesting active recruitment of macrophages and other inflammatory cells.

There is mounting evidence that macrophage invasion may be a causal factor in rupture. Frosen *et al*.[60] found more prominent macrophage infiltration in ruptured aneurysms compared to that found in unruptured aneurysms. Of particular interest was the infiltration of macrophages observed within the first 12 h after rupture, suggesting that macrophages may induce the rupture. MRI investigations of aneurysms with ferumoxytol (AMAG Pharmaceuticals, Lexington, Massachusetts, USA), a superparamagnetic iron oxide particle cleared by macrophages, have also linked macrophage infiltration with rupture.[111-113] In a study of 48 unruptured aneurysms, all aneurysms that showed early uptake of ferumoxytol on MRI ruptured within 6 months.[114] Among aneurysms demonstrating late uptake, there were no ruptures or increase in size during the follow-up period. Immunohistochemical analysis found greater levels of inflammation in aneurysms with early uptake of ferumoxytol. The authors propose that early uptake of ferumoxytol is associated with more prominent inflammation, increased macrophage infiltration, and thus, a greater risk of rupture. Follow-up investigations utilizing aspirin as an anti-inflammatory agent found a decrease in aneurysm wall signal intensity on ferumoxytol MRI and a diminished number of macrophages on immunostaining.[111] Hasan *et al*.[106] examined the M1 (pro-inflammatory) and M2 (anti-inflammatory) subsets of macrophages in a population of ruptured and unruptured clipped aneurysms. While M1 and M2 macrophages were observed in equal proportions in unruptured aneurysms, M1 macrophages were found in a significantly greater proportion in ruptured aneurysms.

Therapeutic implications

Current treatment options for ruptured and unruptured cerebral aneurysms include microsurgical and endovascular obliteration. These interventions are associated with a significant morbidity and mortality, the risk that is magnified in cases of asymptomatic unruptured aneurysms. Thus, study of the mechanisms underlying aneurysm evolution is critical to establish a better understanding of which aneurysms are more likely to rupture. Additionally, this data may provide insight into the biological pathways best-suited for pharmacological intervention, stabilization of the aneurysm wall, and prevention of rupture. The

inflammatory process appears to possess multiple targets ideally suited for such pharmacological treatment.

The wide range of pro-inflammatory pathways induced by TNF-α makes this cytokine an attractive target for blockade.[2] Preservation of endothelial function, maintenance of the VSMC contractile phenotype, and inhibition of inflammatory cell migration are all potential benefits of TNF-α antagonism. MMP-2 and MMP-9 blockade has proven to limit aneurysm development in animal models, possibly identifying an additional mechanism with clinical relevance.[51] Modification of VSMC phenotype continues to be an area of interest, with both cytokine and transcription factor-mediated changes representing possible therapeutic targets.[102] Macrophages represent an additional cellular target for pharmacologic intervention. Hasan *et al*.[113] has already shown aspirin to potentially decrease the risk of aneurysm rupture, a clinical benefit possibly derived from diminished macrophage infiltration of the aneurysm wall. Nakakoa *et al*.[115] has demonstrated gene expression profiles in ruptured aneurysms that indicate the macrophage-mediated inflammation as a key contributor to aneurysm rupture. Future studies may determine these identified genes as diagnostic markers for aneurysms prone to rupture or potential therapeutic targets. Importantly, in all of these areas the therapeutic benefit must be weighed against the risks of altering what, in many instances, is a natural and protective biological response.[2]

CONCLUSION

Cerebral aneurysms remain a significant health and socioeconomic problem, with the majority of ruptures leading to death or severe disability. Microsurgical and endovascular interventions represent the two modalities of treatment; however, both are associated with risk. An understanding of the mechanisms leading to aneurysm development is necessary to identify markers predictive of growth and rupture, as well as targets for pharmacologic intervention. Through multiple pathways, the inflammatory response appears to drive the initiation of aneurysm formation, potentiate continued growth, and contribute to eventual rupture. Animal and human studies highlight the complex interaction between the endothelium, VSMCs, and inflammatory cells. Phenotypic change, cytokine production, apoptosis, and cellular migration all partake in aneurysm evolution. Delineation of those at greatest risk for rupture would afford improved patient selection with regards to aneurysm obliteration. Furthermore, the definition of these various processes may hold promising pharmacological therapeutic implications in the future.

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